UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/574,461	11/30/95	BARONE A	16528X-0155-

HM21/0429

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EXAMINER	
RICIGLIANO,J	
ART UNIT	**PAPER NUMBER**
1648	16

DATE MAILED: 04/29/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

☆U.S.GOVERNMENT PRINTING OFFICE 1995-319-826

Office Action Summary

Application No.	Applicant(s)
08/574,461	Bar ne et al.
Examiner	**Group Art Unit**
J s ph W. Ricigliano Ph. D.	1648

☒ Responsive to communication(s) filed on *Feb 9, 1998*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-15, 37, and 38* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-15, 37, and 38* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachm nt(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Amendments Entered

Applicants', declaration and extension of time filed 2/4/98 have been received and entered.

Claims 37 and 38 have been entered.

Claims 1-15, 37 and 38 are pending.

Election/Restriction

1. Applicants' election without traverse of claims 1-15 in Paper No. 10 is acknowledged.

Claim Objections

In view of applicants corrections, the objection to claim 2 for informal matters is withdrawn.

Rejections Under - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was

2. Claim 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds et al. in view of Pease et al for reasons of record in paper 12.

Response to Arguments

3. Applicants' arguments filed 2/4/98 have been fully considered but they are not persuasive for the following reasons:

4. Claim 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds *et al.* in view of Pease *et al.*for reasons of record in paper 12.

With respect to applicants arguments that the Reynolds *et al* in view of Pease *et al* do not provide a prima facia case the examiner notes the following:

With respect to the method of claim 1 which is comprised of three steps

i) Providing a preselected array of polymers on a soilid support is taught by Pease *et al.* (see for example figure 4.). Moreover, an array of preselected nucleotides on a solid substrate could be two or more of the 9 MP-oligonucleotides synthesized in Scheme III with a standard synthesizer using CPG supports (control pore glass, which reads on a solid support) by Reynolds *et al* prior to cleavage (See page 369, col 1). Since all of the bases in the oligo nucleotides of array absorb strongly in the UV any base constitutes a UV detection label.

ii) Cleaving the array is taught by Reynolds. Reynolds *et al* teach that labeled nucleotides can be cleaved from the solid supports (page 370 column 2). Moreover, a cleavable linker could be a restriction endonuclease site incorporated into the nucleotide sequences of either Reynolds *et al.* or Pease *et al.*

iii) Reynolds *et al* also teach that the nucleotides of their invention could be detected by coupling to psoralen and detection by HPLC at 340 nm (page 371, column 1)

Therefore, Reynolds *et al* in view of Pease *et al* teach all of the limitations of claim 1.

One of ordinary skill in the art would recognize that the single isomer limitation of claim 2 and the heterogeneous size limitation of claim 4 could be met by controlling the number of cycles and reagents employed in the synthetic in the synthesis apparatus of Pease or Reynolds *et al.*

Reynolds also teaches the use of HPLC and PAGE for the separation of labeled oligonucleotides. While Reynolds *et al* use reverse phase HPLC for their applications (page 367 col 1, for example) choosing to use a sizing column or an ion exchange column in place of reverse phase HPLC the separation would be obvious to of one of ordinary skill in the art. Moreover, separations using PAGE as in figure 1 (which reads on electrophoretic separations) separate based upon size and mass and the capillary gel separation format of claim 5 is obvious in view of the slab gel format employed by Reynolds *et al.*

The specific limitation of claim 10 and its dependent claims, providing a reference array (which reads on a control group) is fundemental to the application of the scientific method. One of ordinary skill in the art would not attempt to design any experiment without incorporating the appropriate control groups in order to account for experimental variability. Moreover, one of ordinary skill in the art would not attempt to alter more than one variable at a time, the specific limitation of claim 12.

Applicants' assertions concerning lack of motivation and use of hindsight in combining the reference have been fully considered and not found persuasive.

Applicants' assertion of lack of motivation and use of hindsight in combining the references on page 3 of their response. However, applicant continues on page 4 with the argument that Pease uses the incorporation of a fluorescently labeled probe to determine coupling efficiency. This in fact goes to the center of the claimed invention: Claim 1 "A method of monitoring polymer array synthesis," since coupling efficiency is critical to array synthesis. Moreover, applicants' argument that the cleavage of the array would destroy the array for its intended purpose is narrowly conceived. One of ordinary skill would recognize that more than one linker could have been used such that release of only a portion of each member of the array for analytical purposes was done, thereby leaving the array still intact for other use. Alternatively, cleavage and analysis of the array components following its use in detecting sequences may be done as the last portion of protocol for quality control purposes to ensure the array was appropriately synthesized; especially if negative results were reported. While the a array would be destroyed in this alternative scenario, it would have already fulfilled the purpose applicant appears to believe it is limited to. Therefore, it would appear that neither hindsight nor lack of motivation were involved in the formulation of the rejection.

Additional Claim Rejections - 35 USC § 103

5. Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds *et al* in view of Pease *et al.*

See the teachings of Reynolds *et al.* in view of Pease *et al* as applied to claims 1-15 under 35 USC 103(a) in paper 12. It is noted that the incorporation of fluorescent phosphor-amidate labels (FAM phosphoramidate, pg 5024) into oligonucleotides was taught in Pease which reads on a polymer comprised of a fluorescent label. Detection of fluorescently labeled DNA by imaging such as in Pease figure 2 is known in the art.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to utilize a fluorescent label to tag and detect oligonucleotides cleaved from an array because Pease *et al* taught the incorporation of fluorescent phosphoramidate labels into oligonucleotides and Reynold taught the use of HPLC to separate and detect oligonucleotides from an array. One of ordinary skill in the art would have been motivated to do so in order to increase the sensitivity of detection afforded by fluorescent labels. One of ordinary skill in the art would have expected that the stable incorporation of the labels into the oligonucleotides of an array would be successful because Pease had previously accomplished this employing FAM phosphoramidate.

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph W. Ricigliano Ph. D. whose telephone number is (703) 308-9346. The examiner can normally be reached on Monday through Thursday from 7:30 A.M. to 5:00 P.M. and alternate Fridays from 7:30 A.M. to 5:00 P.M.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist whose telephone number is (703) 308-0196.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald Adams, can be reached at (703) 308-0570.

Joseph W. Ricigliano Ph. D.

LORA M.
PRIMARY EXA
GROUP